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Original article

Validation of the total dysphagia risk score (TDRS) in head and neck cancer patients in a conventional and a partially accelerated radiotherapy scheme

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Abstract

Background and purpose

A risk model, the total dysphagia risk score (TDRS), was developed to predict which patients are most at risk to develop grade ⩾2 dysphagia at 6 months following radiotherapy (RT) for head and neck cancer. The purpose of this study was to validate this model at 6 months and to investigate the power at earlier and later time-points. A second aim was to see if this model can be used in a partially accelerated RT regimen.

Materials and methods

164 patients from 3 different centres treated with RT between 2008 and 2014 were included in the current study. Both physician-scored dysphagia and QoL data were prospectively obtained. The TDRS of all patients was correlated with the physician-scored dysphagia and the QoL data. To validate this prediction model, we tested the validity in terms of calibration and discrimination.

Results

Partial acceleration had no influence on the TDRS. Regarding physician-scored dysphagia, there was a significant correlation with dysphagia grade ⩾2 at 1, 3, 6 and 9 months. The area-under-the-curve at 1 month was 0.85; at 3 months 0.80; at 6 months 0.85; at 9 months 0.86 and 0.79 at 12 months. Regarding QoL, TDRS correlates with PEG-tube usage at 6 and 12 months.

Conclusion

We found significant correlations between TDRS and dysphagia grade ⩾2 and PEG-tube usage.

Keywords: Radiotherapy; Head and neck cancer; Dysphagia; Total dysphagia risk score; Quality of life

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world. Radiation therapy (RT) with or without concurrent chemotherapy (CT) has emerged as the treatment of choice for patients with locally advanced HNSCC.

The use of altered RT fractionation schedules and the addition of concurrent CT to the management of HNSCC have significantly increased both loco regional control and overall survival [1,2]. However this came at the cost of more treatment related toxicity, especially xerostomia and dysphagia [3–5]. Dysphagia has a strong negative impact on health-related quality of life (QoL) during and after treatment [3].

Predicting which patients are at risk for developing severe dysphagia can help to select patients who might benefit from a preventive percutaneous endoscopic gastrostomy (PEG)-tube placement before the start of treatment [3–7].

In 2009, the total dysphagia risk score (TDRS), a risk model for assessing the risk to develop dysphagia after RT for HNSCC, was created. The following independent prognostic factors for swallowing dysfunction at 6 months were found and incorporated into this model: (1) T3–T4, (2) bilateral neck irradiation, (3) weight loss prior to radiation, (4) oropharyngeal and nasopharyngeal tumours, (5) treatment modality: accelerated RT and concomitant chemoradiation (CRT). The aim of the authors was to find a risk model to predict dysphagia at 6 months ($SWALL_{6months}$). Based on the TDRS, 3 risk groups to develop dysphagia could be defined (low-, intermediate- and high-risk patients). Until now, this risk model was only validated retrospectively by one research group for acute dysphagia, in a small patient cohort (47 patients) [8].

The aim of this study was to prospectively validate this risk model as a predictive measure for *physician-scored* and *patient-scored (QoL) dysphagia at 6 months*. Since in one of the participating centres a partially accelerated RT schedule was used, we also investigated how partial acceleration needs to be scored in the TDRS. Furthermore, we wanted to investigate the predictive power of this model at 1, 3, 9 and 12 months of follow-up.

Material and methods

Patient data

We collected data from 270 patients from 3 different centres treated between 2008 and 2014. All patients were diagnosed with HNSCC originating from the oral cavity, oropharynx, larynx or hypopharynx and were included in prospective randomized trials on de-escalation in the elective neck. Patient work-up was done according to institutional guidelines. The decision for primary (C)RT or surgery followed by postoperative (C)RT with curative intent had to be made by the multidisciplinary board meeting at each participating centre. All patients gave written informed consent. Patients were excluded according to the same criteria as used in the original paper (Fig. 1) [1]. Patients who received concurrent cetuximab were excluded from the present study. The most important pre-treatment characteristics are listed in Table 1.

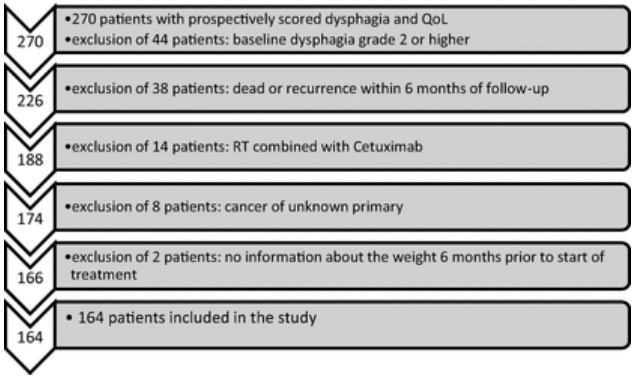

Fig. 1 Inclusion and exclusion of patients according to the criteria of the original article [1].

Table 1 Patient characteristics.

Average age	59.9 year
Median age	59 year (range 38–83 year)
Male	134 (81.7%)
Female	30 (28.3%)

T1	6 (3.7%)
T2	57 (34.8%)
T3	55 (33.5%)
T4	46 (28.0%)
N0	43 (26.2%)
N1	22 (11.3%)
N2	95 (57.9%)
N3	4 (2.4%)
Baseline swallowing	
Grade 0	106 (64.6%)
Grade 1	58 (35.4%)
Weight loss at baseline	
No weight loss	108 (65.8%)
1–10%	50 (30.5%)
>10%	6 (3.7%)
Tumour subsites	
Larynx	35 (21.3%)
Oropharynx	77 (47.0%)
Oral Cavity	24 (14.6%)
Hypopharynx	28 (17.1%)
Bilateral neck irradiation	164 (100%)

Treatment

All patients were treated with intensity modulated RT (IMRT). For target volume definition, a planning-CT scan was used. The overall treatment time ranged between 40 days and 51 days. Different RT schedules were applied according to the habits of the individual treatment centres (Table 2). RT was delivered 5 days a week.

Table 2 Different RT schemes of our study population.

Conventional fractionation	
70 Gy/2 Gy	11 patients
69.12 Gy/2.16 Gy	41 patients
66 Gy/2.2 Gy	25 patients

69 Gy/2–3 30 Gy	3 patients
Hyperfractionation schedule	
40 Gy/2 Gy (once daily) + 32 Gy/1–2 6 Gy (twice daily)	75 patients
Postoperative radiotherapy	
66 Gy/2 Gy	3 patients
69–72 Gy/2–3 16 Gy	6 patients
Adaptive radiotherapy using 2 treatment adaptations	30 patients
PTV elective nodal volume EQD2	
50 Gy	48 patients
40 Gy	116 patients

A hyperfractionated accelerated fractionation schedule was given to 75 patients. A total dose of 72 Gy was delivered in an overall treatment time of 6 weeks: twenty daily fractions of 2 Gy (40 Gy), 5 times a week, followed by 20 fractions of 1.6 Gy twice daily (32 Gy).

Nine patients underwent a tumour resection prior to RT. 30 patients were included in a study with adaptation of the treatment after 2 and 4 weeks into treatment.

Concomitant CRT was given in 110 patients. CRT consisted of cisplatin 100 mg/m^2 three weekly or cisplatin 40 mg/m^2 weekly.

Scoring

Dysphagia was scored prospectively according to the RTOG/EORTC Acute and Late radiation morbidity scoring. QoL was assessed with the EORTC QLQ-C30 and the head and neck cancer module, the EORTC QLQ-H&N35 questionnaire at 6 months and at 12 months. We chose to correlate global health status, appetite loss, pain, swallowing, trouble with social eating, the use of nutritional supplements, feeding tube usage and weight loss with the TDRS risk groups.

Since all patients were included in a study protocol, follow-up after radiotherapy was done uniformly every two months for the first 2 years.

Statistics

To validate the TDRS, we tested model performance in terms of calibration and discrimination.

As a first step, we calculated the TDRS for every patient. We defined the weight loss as the percentage of total body weight lost during the 6 months prior to RT. The TDRS was scored as described in the original paper [3].

In the original manuscript, there were however no patients who were treated with a combination of partially accelerated radiotherapy and chemotherapy. To decide which scoring we had to give to these patients, we searched for the best fit testing calibration-in-the-large. In the original article chemotherapy was scored as 5 points, and accelerated radiotherapy was scored as 6 points. Therefore we chose to calculate the TDRS of patients who received accelerated RT combined with CT first as 5 (no added effect of the partially accelerated RT) and later on as 6. One previous article scored concomitant partial accelerated RT and CT as 5 points; however without mentioning why [8].

Afterwards, we calculated the expected risk for every patient individually using the original article [3]. The mean expected risks were later on compared with the observed prevalence of RTOG 2–4 dysphagia in our patient population. We tested the calibration-in-the-large first using 5 points to score partially accelerated RT and CT, and later on using 6 points to score partially accelerated RT and CT in order to define the best fit and the best scoring method.

Furthermore, the Hosmer–Lemeshow goodness of fit test was used to assess whether or not the observed event rates match the expected event rates in consecutive subgroups of the model population.

Finally, the prediction capability of the TDRS was assessed. Using a logistic regression model, receiver operator characteristic curves (ROC) were plotted to test discrimination in terms of area under the curve (AUC) to evaluate the predictive capability of the model. A *p*-value of less than 0.05 was taken to indicate statistical significance. These analyses were performed using STATISTICA. Quality of Life data were handled as described by the EORTC guidelines.

Results

The prevalence of grade 2–4 RTOG swallowing dysfunction ($RTOG_{G2\text{-}4}$) decreased over time. The prevalence of $RTOG_{G2\text{-}4}$ was 55,2% (90 of 163 patients at risk) at 1 month ($SWALL_{1month}$), 31,3% (51 of 164 patients at risk) at 3 months ($SWALL_{3months}$), 20,1% at 6 months (33 of 164 patients), 11% (17 of 154 patients at risk) at 9 months ($SWALL_{9months}$) and 6,3% (7 of 112 patients at risk) at 12 months ($SWALL_{12months}$). There was no prospectively scored RTOG swallowing dysfunction for one patient at 1 month, for 10 patients at 9 months and for 42 patients at 12 months. The relationship between the three risk groups and the prevalence of $RTOG_{G2\text{-}4}$ at 1 and 6 months are listed in the Appendix.

After calculation of the TDRS, five patients were classified in the low-risk group (TDRS 0–9); 54 patients in the intermediate-risk group (TDRS10–18) and 105 patients in the high-risk group (TDRS > 18).

Firstly, we used 5 points to score partially accelerated RT combined with CT, this would mean that there is no effect of partial acceleration. We found an expected risk to develop RTOG 2–4 dysphagia at 6 months of 32% (95% CI 17–43%). The observed RTOG 2–4 dysphagia at 6 months in our patient group was 20,1%, thus within this 95% CI.

When we used 6 to score partially accelerated RCT, our results were not within this 95% CI. Therefore, we used 5 points for the scoring in the second part of our study for partially accelerated RT with concomitant CT.

Our population was divided into 10 groups using the Hosmer–Lemeshow test. The mean risks and the observed prevalence were correlated at all 5 time points. We found a non-significant *p*-value at all 5 time points, indicating no evidence of poor fit of the TDRS (i.e. no significant difference between predicted and observed prevalences).

At 1 month, there was a significant correlation between the TDRS and $RTOG_{G2\text{-}4}$ ($p = 0.001$). This was also observed at 3 ($p = 0.001$) and 6 months ($p = 0.001$). At 9 months we saw a borderline significant correlation ($p = 0.05$). At 12 months the correlation was not significant. The AUC at 1 month was 0.85 (95% confidence interval: 0.78–0.89); at 3 months 0.80 (95% confidence interval: 0.77–0.84); at 6 months 0.85 (95% confidence interval: 0.79–0.90) (Fig. 2); at 9 months 0.86 (95% confidence interval: 0.80–0.91) and 0.79 (95% confidence interval: 0.72–0.84) at 12 months.

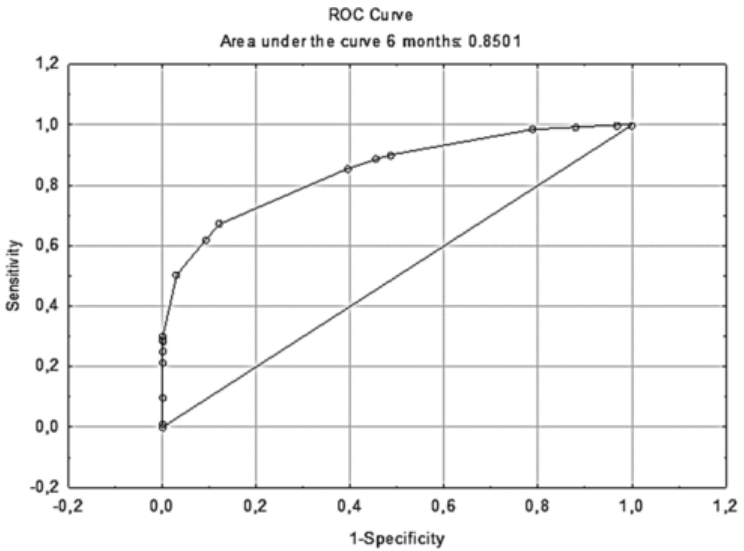

Fig. 2 ROC (receiver operator characteristic) curve to evaluate the prediction capability of the TDRS for grade 2 or higher late swallowing dysfunction at 6 months.

Global health status, appetite loss, pain, swallowing problems, trouble with social eating, the use of nutritional supplements and weight loss at 6 and 12 months were not significantly correlated with the risk groups of the TDRS. The use of a feeding tube was significantly correlated with the risk groups of the TDRS at 6 months ($p = 0.017$). At 12 months, the correlation was borderline significant ($p = 0.050$).

Discussion

Dysphagia remains a major problem for patients treated witch (C)RT for locally advanced HNSCC. Dysphagia leads to longer eating times, inability to eat different types of food, and fear or inability to eat in public which in turn results in social isolation and depression. The TDRS is a way to predict dysphagia at 6 months [10].

In the original TDRS paper, a conventional fractionation and accelerated fractionation schedule was applied [3]. In our study 75 patients received a hyperfractionated *partially accelerated fractionation schedule* [11]. For patients who

received partially accelerated RT with concurrent CT and the score of 0 for partially accelerated RT without concurrent CT, proved to be the best fit. This is in line with the study of Konwai et al. In that study, six patients who underwent partially accelerated RT, were also allocated to 5 points when concurrent CT was given [8]. However in this study the authors do not clarify why 5 points were given.

Besides the problem of the scoring of partial acceleration, we observed a second problem in our patient cohort; the scoring of the administration of *cetuximab*. In the original TDRS paper, no patients were treated with cetuximab [3]. Although the RCT suggested that the addition of cetuximab to RT does not increase dysphagia, we excluded this subgroup of patients because of a possible negative bias [12,13]. Patients who received cetuximab in the participating centres could not receive CT because of morbidity and general health status. These morbidities might influence the dysphagia scoring.

A third problem that we encountered using TDRS score, was *weight loss* prior to RT. In the original paper, there was no definition of the time period of weight loss, neither how weight loss due to surgery should be handled [3]. We chose to compare the weight at the start of RT with the weight 6 months prior to start. This definition can however have repercussions on the scoring. A small difference in measured weight (0 or 1% loss) makes a difference of 5 points on the total TDRS score (Appendix). Those 5 points can lead to a different category (low, intermediate, high risk to develop dysphagia).

Our observed dysphagia rates are in line with the ones described by Konwai et al. and Langendijk et al. [3,8]. However, we only identified 5 patients in the low risk group. A possible explanation is that all our patients received a bilateral neck irradiation (scored 9 points). At 12 months we did not observe a significant correlation, whereas at the other time points the correlation is significant. A possible explanation is that there were only 7 patients out of 112 patients with a $RTOG_{2-4}$ at 12 months. The TDRS model was developed to predict $RTOG_{2-4}$ at 6 months of follow-up. The authors of the original paper did not develop nor test the model for later or earlier time points, but showed that there was a correlation between $RTOG_{2-4}$ at 6 months and at later time points. This is the first paper to test this model at 1, 3, 9 and 12 months in a prospective way. Since our population consists of only 164 patients, it is important to say that these results at other time-points than 6 months are only exploratory and should be further validated.

To appreciate if the observed significant correlations were not a coincidence we performed a ROC analysis. AUC's at the different time points ranged between 0.79 and 0.86, indicating a good predictive value of the model. Whether this means that the TDRS can be used to take predictive measures is however not clear.

Firstly it remains unclear from which preventive measurements patients would benefit the most. The impact of PEG use on swallowing and swallowing-related outcomes remains unclear. Some researchers have suggested that PEG use may negatively affect the swallowing physiology, function and/or quality of life. A recent published review of twenty studies could not clarify this either [14]. On the other hand, recently, a prospective randomized trial was set up to evaluate the impact of prophylactic swallowing exercises on swallowing-related outcomes in HNSCC patients treated with curative RT [15]. There was no difference between the two groups (standard care versus home swallowing exercises) on the dysphagia outcomes during and after treatment. The authors of the paper blame this on poor adherence to exercises and dropouts. The best intervention method to lower dysphagia is thus currently unknown.

Secondly, using the TDRS, we would still take preventive measures in patients who do not necessarily need it. Our ROC-analysis resulted in 70% specificity for 80% sensitivity indicating a reasonable rate of detecting patients that would benefit from an intervention, but also a substantial group of patients that will not need such an intervention. Therefore we do not recommend to use this model to select patients who might benefit from PEG-tube placement before the start of treatment, since PEG tube dependency was not the endpoint of the TDRS model. Recently, however, 2 models were published by Wopken et al. to predict PEG tube dependency at 6 months. Interestingly the first model uses comparable parameters as the TDRS score does (T, weight loss at baseline, bilateral neck irradiation and treatment modality). A difference is that also nodal stage is taken into consideration in this model [16]. The second model, however, also included radiotherapy plus cetuximab and the mean dose to the superior and inferior pharyngeal constrictor muscle, to the contralateral parotid gland and to the cricopharyngeal muscle [17].

Regarding QoL, only PEG-usage correlated with TDRS at 6 months and borderline at 12 months. Other QoL items were not significantly correlated. In the past, studies on the correlation between patient-rated dysphagia and objective assessments of dysphagia showed conflicting results [1,3]. A possible explanation can be that QoL scoring in HNSCC patients, who are known to be frail and often have a low socio-economic status, can be challenging.

The strength of this article is that all scores (physician- as well as patient rated by QoL) were prospectively gathered, in contrast to the previous validation study were the morbidity was retrospectively scored based on the medical records [8].

We are aware that the RT schemes of our study population are very diverse. However our results indicate that TDRS can be used with different RT schemes. Above all, the TDRS is easy to use in daily clinical practice and might guide clinicians in identifying patients who might benefit from additional attention to swallowing problems during (C)RT and follow-up.

The TDRS has been validated for predicting physician-scored swallowing dysfunction induced by (C)RT at 6 months. Moreover, we found significant correlations between TDRS and $RTOG_{G2-4}$ at 1, 3, 6 and 9 months, with acceptable AUC's.

We found that this predictive model can also be used with a partially accelerated RT scheme; the partial acceleration does not have to be taken into account. Regarding QoL, we found a correlation between PEG-tube usage at 6 and 12 months.

Conflict of interest statement

Daan Nevens is supported by a grant from VLK (Vlaamse Liga tegen Kanker) and Koning Boudewijnstichting (the Anhaive cancer fund).

Uncited reference

[9].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.10.008.

References

[1]

J. Bourhis, J. Overgaard, H. Audry, et al., Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis, *Lancet* **368**, 2006, 843–854.

[2]

J. Pignon, A. le Maitre, E. Maillard, et al., Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients, *Radiother Oncol* **92**, 2009, 4–14.

[3]

J.A. Langendijk, P. Doornaert, D.H. Rietveld, I.M. Verdonck-de Leeuw, C.R. Leemans and B.J. Slotman, A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer, *Radiother Oncol* **90**, 2009, 189–195.

[4]

N. Platteaux, P. Dirix, E. Dejaeger and S. Nuyts, Dysphagia in head and neck cancer patients treated with chemoradiotherapy, *Dysphagia* **25**, 2010, 139–152.

[5]

I.M. Verdonck-de Leeuw, L.M. Buffart, M.W. Heymans, et al., The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: a prospective cohort study, *Radiother Oncol* **110**, 2014, 1–7.

[6]

S. Servagi-Vernat, D. Ali, C. Roubieu, C. Durdux, O. Laccourreye and P. Giraud, Dysphagia after radiotherapy: state of the art and prevention, *Eur Ann Otorhinolaryngol Head Neck Dis* **132**, 2015, 25–29.

[7]

J.A. Langendijk, P. Doornaert, D.H.F. Rietveld, I.M. Verdonck-de Leeuw, C. René Leemans and B.J. Slotman, A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer, *Radiother Oncol* **90**, 2009, 189–195.

[8]

K. Koiwai, N. Shikama, S. Sasaki, A. Shinoda and M. Kadoya, Validation of the total dysphagia risk score (TDRS) as a predictive measure for acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers, *Radiother Oncol* **97**, 2010, 132–135.

[9]

E.W. Steyerberg, F.E. Harrell, G.J.J.M. Borsboom, M.J.C. Eijkemans, Y. Vergouwe and J.D.F. Habbema, Internal validation of predictive models: efficiency of some procedures for logistic regression analysis, *J Clin Epidemiol* **54**, 2001, 774–781.

[10]

S. Nuyts, M. Lambrecht, F. Duprez, et al., Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity, *Radiother Oncol* **109**, 2013, 323–329.

[11]

S. Nuyts, P. Dirix, P.M.J. Clement, et al., Impact of adding concomitant chemotherapy to hyperfractionated accelerated radiotherapy for advanced head-and-neck squamous cell carcinoma, *Int J Radiat Oncol Biol Phys* **73**, 2009, 1088–1095.

[12]

J.A. Bonner, P.M. Harari, J. Giralt, et al., Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck, *N Engl J Med* **354**, 2006, 567–578.

[13]

D. Curran, J. Giralt, P.M. Harari, et al., Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab, *J Clin Oncol* **25**, 2007, 2191–2197.

[14]

S.M. Shaw, H. Flowers, B. O'Sullivan, A. Hope, L.W.C. Liu and R. Martino, The effect of prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement on swallowing and swallow-related outcomes in patients undergoing radiotherapy for head and neck cancer: a systematic review, *Dysphagia* **30**, 2015, 152–175.

[15]

H.R. Mortensen, K. Jensen, K. Aksglæde, K. Lambertsen, E. Eriksen and C. Grau, Prophylactic swallowing exercises in head and neck cancer radiotherapy, *Dysphagia* **30**, 2015, 304–314.

[16]

K. Wopken, H.P. Bijl, A. van der Schaaf, et al., Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer, *PLoS ONE* **9**, 2014, e94879.

[17]

K. Wopken, H.P. Bijl, A. van der Schaaf, et al., Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer, *Radiother Oncol* **113**, 2014, 95–101.

Appendix A. Supplementary data

Multimedia Component 1

Appendix This file contains supplementary material.

Queries and Answers

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